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Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort

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Background: Treatment of multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection presents a challenge because of the scarcity of available options. Even though combination therapy (CT) is frequently used in clinical practice, data are needed to support its use instead of monotherapy (MT).

Methods: A prospective observational study was conducted in 28 Spanish hospitals. Patients with sepsis caused by MDRAB, defined according to strict criteria, and who received active antibiotic treatment (according to *in vitro* susceptibility testing) for at least 48 h, were included. The main outcome variable was all-cause 30 day mortality after initiation of targeted therapy. Multivariate analysis, including a propensity score (for receiving CT), was performed by Cox regression.

Results: One hundred and one patients were included in the analysis; 68 (67.3%) received MT and 33 (32.7%) received CT. Pneumonia was the most common infection (50.5%), 68.6% of cases being associated with mechanical ventilation. Colistin (67.6%) and carbapenems (14.7%) were the most common drugs used in MT; colistin plus tigecycline (27.3%) and carbapenem plus tigecycline (12.1%) were the most frequent combinations. Crude 30 day mortality was 23.5% and 24.2% for the MT and CT groups, respectively (RR = 1.03; 95% CI 0.49–2.16; $P = 0.94$). Multivariate analysis of 30 day survival showed no trend towards reduced 30 day mortality with CT (HR = 1.35; 95% CI 0.53–3.44; $P = 0.53$). Subgroup analysis showed similar results.

Conclusions: Our data do not support an association of CT with reduced mortality in MDRAB infections. More data for specific types of infection and combinations are needed.

Keywords: *A. baumannii*, combination treatment, antimicrobial resistance, healthcare-associated infections, nosocomial pneumonia

Introduction

During the last decade, the rate of nosocomial infections caused by multidrug-resistant *Acinetobacter baumannii* (MDRAB) has increased in several areas of the world.[1–3] According to European surveillance data from 2009, *Acinetobacter* spp. were implicated in up to 21.8%, 17.1% and 11.9% of episodes of intensive care unit (ICU)-acquired pneumonia, ICU-acquired bloodstream infections and ICU-acquired urinary tract infections, respectively.[3] Data from a systematic review showed that attributable mortality in patients with infections ranged from 7% to 23% in ICU patients and from 10% to 43% in patients on conventional wards.[4]

Carbapenems and sulbactam are the usually recommended drugs for the treatment of invasive infections.[1–3,5] However, resistance to carbapenems has been increasing over the last decade. The best treatment for infections caused by carbapenem-resistant isolates has not been established. Observational data have suggested that colistin monotherapy (MT) is as effective as carbapenems against carbapenem-susceptible isolates,[6,7] although suboptimal dosing of colistin and the presence of

heteroresistant strains (>40% in some studies) may be associated with a higher rate of treatment failure.[8] The objective of this study was to assess the clinical efficacies of MT and combination therapy (CT) in MDRAB sepsis.

Methods

Study design and patients

A prospective observational study was conducted in 28 Spanish hospitals, 21 of them with >500 beds, between 1 February and 31 March 2010. Adult patients (>18 years) from whom *A. baumannii* was isolated in any clinical sample, identified by daily review of microbiology reports at the participating centres, were eligible. We included those who met the following criteria: (i) an infection caused by *A. baumannii* was diagnosed (see definition below); (ii) sepsis criteria were present; and (iii) the patient received treatment with at least one drug active *in vitro* for at least 48 h following the clinical diagnosis of infection. Exclusion criteria included missing data on treatment, <30 days of follow-up, and patients treated in MT with antibiotics not considered first-line for the specific infection, such as aminoglycosides (except for urinary tract infection or tigecycline for patients with pneumonia or urinary tract infection).[9–11] Treatments were decided by

Table 1. Features of patients with MDRAB infection

Variable	All patients (*n*=101)	MT (*n*=68)	CT (*n*=33)	*P*
Age (years), median (IQR)	60 (52–75)	60 (49–74)	61 (64–77)	0.41
Female	38 (37.6)	24 (35.3)	14 (42.4)	0.49
Comorbidities				
diabetes mellitus	20 (19.8)	11 (16.2)	9 (27.3)	0.19
chronic pulmonary disease	14 (13.9)	8 (11.8)	6 (18.2)	0.38
malignancy	16 (15.8)	15 (22.1)	1 (3)	0.01
dialysis treatment	3 (3)	1 (1.5)	2 (6.1)	0.20
immunodeficiency	22 (21.8)	17 (25)	5 (15.2)	0.26
Age-weighted Charlson comorbidity index, median (IQR)	3 (2–6)	3 (2–7)	3 (2–6)	0.45
Pitt score, median (IQR)	4 (1–6)	4 (1–6)	4 (0–6)	0.68
Present ICU admission	63 (62.4)	43 (63.2)	20 (60.6)	0.80
Predisposing factors				
mechanical ventilation	49 (48.5)	32 (47.1)	17 (51.5)	0.67
central venous catheter	72 (71.3)	49 (72.3)	23 (69.7)	0.81
major surgery	33 (32.7)	23 (33.8)	10 (30.3)	0.72
previous antibiotic treatment	87 (86.1)	57 (83.8)	30 (90.9)	0.33
Severe sepsis or septic shock	42 (41.6)	30 (44.1)	12 (36.4)	0.46
Hospital-acquired[a]	91 (90.1)	62 (91.2)	29 (87.9)	0.60
Previous hospital stay, median (IQR)	12 (7–21)	12 (6–23)	11 (7–19)	0.47
Source of infection				
respiratory tract[b]	61 (60.4)	40 (58.8)	21 (63.6)	0.64
skin and soft tissue	13 (12.9)	8 (11.8)	4 (12.1)	0.96
urinary tract	10 (9.9)	9 (13.2)	1 (3)	0.11
intra-abdominal	8 (7.9)	6 (8.8)	2 (6.1)	0.63
others[c]	9 (8.9)	5 (7.4)	4 (12.1)	0.87
Ventilator-associated pneumonia	35 (34.7)	21 (30.9)	14 (42.4)	0.25
Polymicrobial infection	44 (43.6)	30 (44.1)	14 (42.4)	0.87
Bacteraemia	42 (41.6)	24 (35.3)	18 (54.5)	0.07
Susceptibility profile				
MDR	101 (100)	68 (100)	33 (100)	1.0
XDR	5 (4.9)	3 (4.4)	2 (6.1)	0.73
carbapenem-resistant	64 (64)	44 (64.7)	20 (60.6)	0.83
susceptible only to colistin and tigecycline	21 (20.8)	17 (25)	4 (12.1)	0.14
susceptible only to colistin	5 (5)	3 (4.4)	2 (6.1)	0.72
Inadequate empirical treatment	53 (52.5)	35 (51.5)	18 (54.5)	0.77

Data are expressed as number of cases (%) except where specified.
[a]Healthcare-related infections include tracheobronchitis (one case), pneumonia (two cases), skin and soft tissue infection (three cases), urinary tract infection (one case), primary bacteraemia (one case), intra-abdominal infection (one case) and osteoarticular infection (one case).
[b]Pneumonia (51 cases) and tracheobronchitis (10 cases).
[c]CNS infection (one case), osteoarticular infection (one case), primary bacteraemia (five cases) and catheter-related bacteraemia (two cases).

the physicians in charge of the patients. The study was approved by the ethics committee of the Hospital Universitario Virgen Macarena; the need to obtain informed consent was waived given the observational nature of the study.

Variables and definitions

The main outcome variable was all-cause 30 day mortality after the initiation of targeted therapy. As a secondary endpoint, all-cause 14 day mortality was assessed. Therapy with a single antimicrobial agent active *in vitro* was considered to be MT and therapy with two or more active drugs was considered to be CT. Based on previous data,[12–15] any bitherapy that included a carbapenem that was not active *in vitro* was considered as MT when the carbapenem MIC was ≥32 mg/L and as CT when it was lower. For patients whose targeted therapy changed during the course of treatment, we considered only the regimen that was used for at least 50% of the overall treatment duration; if two regimens were used for 50% of the duration, the first administered was chosen.

Acquisition of sepsis was classified as community associated, healthcare associated or nosocomial, following Friedman's criteria.[16] The sources of sepsis were defined according to CDC definitions,[17] modified to ensure that isolation of *A. baumannii* did not represent colonization. In summary, non-sterile samples should fulfil standard criteria for quality, and quantitative cultures were used. The thresholds for considering lower respiratory tract infection were $\geq 10^3$, $\geq 10^5$ and $\geq 10^6$ cfu/mL in protected brush, bronchoalveolar lavage and tracheal aspirate, respectively. Pneumonia, intra-abdominal infections and bacteraemic infections were considered high-risk infection types because they were associated with higher mortality in previous studies.[17–19] The following data were recorded: demographics; comorbidities; severity of underlying condition according to the age-weighted Charlson comorbidity index;[20] neutropenia (granulocyte count <500/mL); immune depression (chemotherapy, radiotherapy, immunosuppressive disease and/or immunosuppressive drugs); recent invasive procedures; acute severity of illness at presentation according to the Pitt score;[21] previous or present ICU admission; and antimicrobial treatments. Empirical therapy was considered inappropriate if no *in vitro* active drug was administered during the first 24 h. Presentation with sepsis was defined according to standard criteria.[22] This analysis was reported following the STROBE recommendations.[23]

Microbiological data

As previously reported,[24] all isolates presumptively identified as *A. baumannii* by local laboratories were sent to a reference laboratory for definitive identification and antimicrobial susceptibility testing by microdilution, following CLSI recommendations;[25] for rifampicin, the Comité de l'Antibiogramme de la Société Française de Microbiologie breakpoint[26] was applied; for sulbactam and tigecycline, isolates with MIC >8 and >1 mg/L, respectively, were considered non-susceptible. Isolates were classified as multidrug resistant (MDR), extensively drug resistant (XDR) and pandrug resistant (PDR) according to Magiorakos *et al.*[27]

Statistical analysis

Univariate comparisons were performed using the χ^2 or Fisher's test for qualitative variables, and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, as appropriate. Because of the limited number of events, multiple multivariate analyses were performed using Cox regression. Variables were selected using a backward stepwise procedure; *P* values <0.2 and <0.1 were used as cut-offs for including variables in or deleting them from the models, respectively. Effect modifications between the exposure of interest and other variables were investigated. A propensity score (PS; the probability of receiving CT) for receiving CT was calculated using a non-parsimonious multivariate logistic regression model for which the outcome variable was use of CT, and included in the models. Variables considered as potentially influencing the prescription of CT included: hospital stay; current or previous ICU admission; duration of previous hospitalization; XDR isolate; age; immunosuppression; cancer; dialysis; mechanical ventilation; prior antibiotic therapy; severe sepsis or septic shock at the time of diagnosis; polymicrobial infection; type of acquisition; source; and bacteraemic infection. This model showed a *P* value of 0.21 with the Hosmer–Lemeshow goodness-of-fit test and an area under the receiver operating curve (ROC) of 0.75, thus showing an acceptable ability to predict CT. The SPSS v17.0 package was used for statistical analysis.

Table 2. Targeted antibiotic regimens used for the treatment of MDRAB

Targeted treatment	Patients, *n* (%)	Crude 30 day mortality, *n* (%)
MT	68	16 (23.5)
colistin	46 (67.6)	12 (26.1)
carbapenem	10 (14.7)	0 (0)
tigecycline	5 (7.4)	1 (20)
sulbactam	5 (7.4)	2 (40)
tetracycline	2 (2.9)	1 (50)
CT	33	8 (24.2)
colistin + tigecycline	9 (27.3)	2 (22.2)
carbapenem + tigecycline	4 (12.1)	2 (50)
colistin + carbapenem	3 (9.1)	0 (0)
colistin + sulbactam	2 (6.1)	2 (100)
colistin + aminoglycoside	2 (6.1)	0 (0)
colistin + rifampicin	2 (6.1)	0 (0)
carbapenem + aminoglycoside	2 (6.1)	1 (50)
tigecycline + rifampicin	2 (6.1)	0 (0)
tigecycline + aminoglycoside	1 (3)	0 (0)
colistin + tigecycline + carbapenem + aminoglycoside	3 (9.1)	0 (0)
colistin + tigecycline + aminoglycoside	2 (6.1)	0 (0)
tigecycline + carbapenem + rifampicin	1 (3)	1 (100)

Results

A. baumannii was isolated from 246 patients during the study period; 150 patients were considered to have an infection; 25 were excluded because they had not received active therapy for at least 48 h, and 24 did not present with sepsis criteria. Therefore, 101 patients were included in the analysis, 68 of whom (67.3%) received MT and 33 (32.7%) CT. Baseline clinical characteristics are shown in Table 1. Sixty-eight percent of pneumonia cases were associated with mechanical ventilation.

Targeted treatments used are shown in Table 2. All survivors received at least 4 days of appropriate treatment. Seven patients received a carbapenem for isolates with an MIC of 16 mg/L combined with another active drug (three combined with tigecycline, one with colistin and three with two or three other drugs), and were considered as receiving CT; a further five patients received a carbapenem for strains for which the MIC was ≥32 mg/L, together with another active antibiotic, and were considered as receiving MT. The dosage of colistin used was the standard at that time (2 MU every 8 h, with adjustment according to renal function) in all but three patients, who received 3 MU every 8 h. Median duration of targeted treatment among survivors was 12 days (IQR 8–17).

Crude 30 day mortality was 23.5% (16/68) in the MT group and 24.2% (8/33) in the CT group (RR=1.03; 95% CI 0.49–2.16; P=0.94) (Table 2). Crude 14 day mortality was 14.7% (10/68) and 15.2% (5/33), respectively (RR=1.03; 95% CI 0.38–2.77; P=0.95). The variables associated with 30 day mortality are shown in Table 3. Multivariate Cox regression analyses are shown in Table 4. Model 1 showed a P value of 0.22 by the Hosmer–Lemeshow goodness-of-fit test, with area under the ROC of 0.77.

Table 3. Univariate analysis of variables associated with 30 day mortality

Variable	Deaths/number exposed (%)	RR (95% CI)	*P*
Age-weighted Charlson comorbidity index			
<5	9 (14.5)	reference	
≥5	15 (38.5)	2.64 (1.29–5.46)	0.006
Type of infection			
urinary tract	0	reference	
upper respiratory tract	4 (40)	4 (0.53–29.80)	0.43
lower respiratory tract	14 (27.5)	2.74 (0.40–18.57)	0.59
skin and soft tissue	3 (25)	2.5 (0.30–20.45)	0.56
abdominal	2 (25)	2.5 (0.27–22.86)	0.30
Bacteraemia			
no	13 (22)	reference	
yes	11 (26.2)	1.18 (0.59–2.39)	0.63
Type of infection according to mortality risk[a]			
low	7 (19.4)	reference	
high	17 (26.2)	1.34 (0.62–2.94)	0.45
Pitt score			
<3	5 (11.6)	reference	
≥3	19 (32.8)	2.81 (1.14–6.94)	0.01
Present ICU admission			
no	7 (18.4)	reference	
yes	17 (27)	1.46 (0.67–3.20)	0.33
Polymicrobial infection			
no	11 (19.3)	reference	
yes	13 (29.5)	1.53 (0.76–3.08)	0.23
XDR *A. baumannii*			
no	23 (24)	1.19 (0.20–7.17)	
yes	1 (20)	reference	0.66
Empirical treatment			
inadequate	8 (15.1)	reference	
adequate	16 (33.3)	2.20 (1.03–4.69)	0.03
Targeted treatment			
MT	16 (23.5)	reference	
CT	8 (24.2)	1.03 (0.49–2.16)	0.94

[a]High-risk types of infection included pneumonia, intra-abdominal infection and any bacteraemic infection.

The variable 'type of infection' was explored in different ways (low- and high-risk types, one specific type versus the rest, etc.), and the results did not differ significantly. Considering all resistant isolates as being classified as MT, the results of Cox regression did not change significantly. Using multivariate model 1, the results were as follows: 14 day mortality, HR 1.5 (95% CI 0.39–5.72), $P=0.55$; 30 day mortality, HR 1.1 (95% CI 0.40–2.90), $P=0.87$.

Finally, we also analysed the impact of CT on 30 day mortality in the following subgroups (HR and 95% CI for mortality with CT are shown): ICU patients, HR=1.25; 95% CI 0.39–4.00; $P=0.71$; patients with pneumonia, HR=1.24; 95% CI 0.32–4.984; $P=0.76$; high-risk types of infection, HR=1.24; 95% CI 0.32–4.84; $P=0.76$; and polymicrobial infection, HR=3.48; 95% CI 0.73–16.67; $P=0.12$.

Discussion

Whether in the crude analysis or after controlling for confounders, we were unable to find any benefit from using CT rather than MT to treat sepsis caused by MDRAB, or alternatively any trend towards a reduced risk of mortality. Similarly, meta-analyses of clinical studies have so far failed to demonstrate any benefit for CT over MT when fully active first-line drugs are used.[28,29] This situation may be different for Gram-negatives showing resistance to all first-line drugs; to take an example, retrospective studies of patients with bacteraemia due to KPC-producing *Klebsiella pneumoniae* showed improved survival when treated with CT compared with MT.[30,31]

With respect to MDRAB, the activity of different combinations has been evaluated in many *in vitro* studies and animal models,[32] although the applicability of the results is doubtful, because the effect of combinations may be strain dependent. However, the potential difference in the effect of combinations according to strains should also be considered in clinical studies. One recent retrospective cohort study found higher mortality among patients treated with colistin MT compared with CT in the crude analysis, although multivariate analysis was not reported.[33] Two randomized controlled trials were recently published that compared colistin versus colistin plus rifampicin in the treatment of ventilator-associated pneumonia[34] and diverse serious infections;[35] although the microbiological eradication rate improved with CT, mortality and cure rates did not. The colistin dose used

Table 4. Multivariate Cox regression models for the impact of CT on 30 day mortality; the PS for CT was included in the models

	HR (95% CI)	*P*
Model 1		
CT	1.35 (0.53–3.44)	0.53
age-weighted Charlson comorbidity index (per unit)	1.19 (1.04–1.47)	0.009
adequate empirical treatment	0.55 (0.23–1.33)	0.19
Pitt score (per unit)	1.15 (1.02–1.29)	0.02
Model 2		
CT	1.43 (0.56–3.67)	0.45
age-weighted Charlson comorbidity index (per unit)	1.23 (1.07–1.42)	0.003
adequate empirical treatment	0.45 (0.17–1.14)	0.09
Pitt score (per unit)	1.17 (1.04–1.34)	0.009
bacteraemia	2.15 (0.79–5.84)	0.13
Model 3		
CT	1.32 (0.52–3.35)	0.56
age-weighted Charlson comorbidity index (per unit)	1.18 (1.04–1.34)	0.009
Pitt score (per unit)	1.17 (1.05–1.32)	0.006
Model 4		
CT	1.26 (0.51–3.19)	0.60
Pitt score (per unit)	1.17 (1.04–1.32)	0.008
adequate empirical treatment	0.55 (0.23–1.34)	0.19
Model 5		
CT	1.52 (0.59–3.92)	0.38
age-weighted Charlson comorbidity index (per unit)	1.20 (1.06–1.37)	0.003
adequate empirical treatment	0.43 (0.18–1.01)	0.05
Model 6		
CT	1.26 (0.51–3.01)	0.62
high-risk source[a]	1.70 (0.58–4.97)	0.33
adequate empirical treatment	0.46 (0.18–1.21)	0.12
Pitt score (per unit)	1.20 (1.06–1.35)	0.004

[a]Pneumonia, bacteraemia and intra-abdominal infection.

in both studies was, as in ours, lower than is presently recommended according to pharmacokinetic/pharmacodynamic studies;[36] an ongoing clinical trial aims to clarify this aspect.[37]

The patients included in our study fitted the general profile of those suffering from *A. baumannii* infections.[2,38] The fact that we included different types of infection made it necessary to control for their effect in the analysis, although it does illustrate the clinical situations that doctors face in actual practice. We included a PS to further control for potential variables that influence the selection of CT. Finally, the study of different patient subgroups showed no trend towards outcome differences between MT and CT.

The high rate of inappropriate empirical treatment should be highlighted. The prognostic impact of appropriate empirical therapy has been described previously and may depend on many variables, including dosage, severity of presentation, source and early source control,[15,16,39] Curiously, the mortality rate of patients who received appropriate empirical treatment was higher in the univariate analysis of our cohort, although the association was reversed in multivariate analysis, indicating the important effect of confounding variables.

In our analysis, we considered any bitherapy that included a carbapenem when the MIC for the strain was $\leq$16 mg/L as CT, according to *in vitro* synergy data between carbapenems and other antibiotics only when the MIC was in that range,[17,18] as well as data from clinical studies.[15,16] However, more data are needed to determine the impact of carbapenems on infections caused by low-level resistant MDRAB isolates.

This study has several limitations. First, as previously stated, it includes several types of infection. Secondly, the CT group was made up of multiple combinations. We did not study other aspects, such as development of resistance or safety. Finally, the sample size may have been insufficient to show any trends in the efficacy of CT or MT, although these data would be useful if additional data from future studies were merged into a meta-analysis. The strengths of the study include the prospective nature of the design, the application of strict criteria when allocating patients to treatment groups, and the use of a PS.

In conclusion, this study was unable to demonstrate clinical or statistically significant differences for preferring MT or CT in the treatment of infections caused by MDRAB. Further studies are needed to better define the potential advantages and disadvantages of CT for these infections. Meanwhile, it seems reasonable to use MT, at least in patients with less severe infections.

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